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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/877,374	06/08/2001	Jeffrey C. Rapp	AVI-007N	2448

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/877,374	RAPP, JEFFREY C.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,9-29 and 62-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7, 9-29, 62-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment, filed 1/27/06, has been entered. Claim 1 has been amended; claim 73 is cancelled; claims 1-5, 7, 9-29, 62-72, are pending and under current examination.

Applicants' provide no specific arguments with regard to the rejections of record, other than that the claims are amended to provide clarity and are neither obvious nor anticipated by the prior art of record.

Note: the claim identifier for claim 69 is listed as "withdrawn", but the claim has been examined, and the Restriction requirement with regard to this claim was withdrawn in the Office action, mailed 6/9/05. Applicants are required to amend this status identifier in response to this Office action.

Claim Rejections - 35 USC § 102

The prior rejection of claim 73 under 35 U.S.C. 102(b) as being anticipated by Heinzel *et al.* or by Carreno *et al.* is withdrawn in view of Applicants' cancellation of the claims.

The prior rejection of claims 1, 2, 4, 5, 7, 9, 11, 12, 14-17, 19-29, 62 and 63 under 35 U.S.C. 102(a) as being anticipated by Ditullio *et al.* is withdrawn, because, Ditullio *et al.* do not specifically teach the isolation of the immunoglobulin from cultured cells, as required by the instantly-amended claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7, 9-17, 19-29, 62 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ditullio *et al.* when taken with Michael *et al.* (cited previously). This is a new grounds of rejection, necessitated by Applicants' amendment to the claims.

The claims as now amended recite that utilizing an avian oviduct cell that is transfected (see claim 1, line 4) and that the immunoglobulin is isolated (claim 1, second to last line).

A blastodermal cell, as taught by Ditullio *et al.* is one that is formed after the fertilization of the ovum and maturation of the ovum. As stated in the Office action, mailed 6/9/05, page 6, this blastodermal cell would be considered generated from the oviduct, and thus, would be considered an oviduct cell (as required by the claims).

Ditullio teach methods of generating transgenic avian. In particular, they teach the introduction of a nucleic acid molecule into the genome of an avian aspecies by contacting *in vivo* a blastodermal cell [see p. 1-2]. The avian species can be, for example, a chicken [see p. 2, lines 9-12]. DiTullio teach that the nucleic acid can contain a sequence encoding an antibody or fragment thereof, for example, a monoclonal antibody, or a chimeric molecule [*e.g.,* containing antibody portions of both murine and human origin] [see p. 2, lines 22-28]. Ditullio discuss the transcriptional regulatory elements that are contained in the nucleic acid construct, such as initiation signals, enhancers, promoters, which induce or control the transcription of protein coding sequences to which they are operably linked [see p. 3, lines 1-5]. For example, the promoter may be constitutive or inducible, and may be tissue-specific, inducible by external signals or within an intron [see p. 3, lines 12-15]. Ditullio teach that the chicken lysozyme or ovalbumin promoter may be used with the described transgene construct [see p. 3, lines 15-17]. In particular, the invention includes a transgene expression cassette in which the heavy and light chain coding regions of an antibody are ligated together, each under the direction of its own promoter operably linked to a matrix attachment region [see p. 3, lines 24-

26]. Ditullio that the avian cell can be targeted either *in vitro* or *in vivo* [see pp. 7-10].

Ditullio differ from the claimed invention in that they do not teach or suggest the expression vector further encodes a second immunoglobulin polypeptide and an IRES, that the vector is a viral vector, and that the promoter is the cytomegaloviral promoter, and they do not teach isolation of the immunoglobulin from the cultured cells. However, prior to the claimed invention, Michael teach producing cells that express monoclonal antibodies, wherein the cells are screened for the antibody of interest, by, for example, measuring the binding of the antibodies (co. 2-3, bridging ¶), and specifically teach *in vitro* transfection of cells, culturing of the cells, and then isolating the antibody from the cells (col. 3, lines 15-27). Furthermore, Michael teach methods of producing monoclonal antibodies in an avian system, and in particular, chickens. They teach that the CMV immediate early gene promoter is a promoter that can be used to obtain high-level of expression of a coding sequence of interest, and that by employing such a well-known promoter, the level and pattern of expression can be optimized (see col. 16, lines 47-63). Michael further teach that the use of IRES elements can create multigene, or polycistronic messages. They teach that IRES elements can be linked to heterologous open reading frames, and that by virtue of the IRES element, multiple genes can be efficiently expressed by a single promoter or enhancer to transcribe a single message [col. 19, lines 5-21]. Michael teach that genetic constructs can be introduced into cells by both viral and non-viral transduction. Viral methods include adenoviral, and adeno-associated viral vectors [col. 19, lines 30-45].

Accordingly, in view of the combined teachings of Michael and Ditullio, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the methods of generating antibodies from avian cells, as taught by Ditullio, by use of the cytomegaloviral promoter, an IRES element, or by use of a viral vector, as well as isolating immunolgloublins produced

by the cultured cells, as taught by Michael, with a reasonable expectation of success. One of ordinary skill would have been sufficiently motivated to make such a modification, because the isolation of antibodies directly from cultured cells would be more efficient, and further, the cytomegaloviral promoter is a well-known and well-characterized promoter that would allow for optimal levels and patterns of gene expression, that utilizing an IRES element would facilitate expression of multiple genes, and that viral transduction is an efficient way to deliver a construct to a cell.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 64-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ditullio *et al.* when taken with Michael *et al.* as applied to claims 1-5, 7, 9-17, 19-29, 62 and 63 above, and further in view of Ling *et al.* **[cited previously]**. This is a new grounds of rejection, necessitated by Applicants' amendment to the claims.

Ditullio *et al.* and Michael *et al.* are described above. They provide the requisite teachings and motivation to produce antibodies from an avian oviduct cell, by culturing a transfected avian oviduct cell and isolating antibodies therefrom.

Ditullio do not specifically teach producing an antibody specific for CTLA4. However, prior to the time the claimed invention was made, Ling teach the sequence of human CTLA4, including its alignment with the mouse CTLA4 sequence. See Figure 3. Ling teach that CTLA4 has been correlated with specific diseases (see p. 341, 2nd column). Najarfian provide the requisite motivation for the production of CTLA4 antibodies, as instantly contemplated. They teach that CTLA-4 is only expressed on activated T-cells, and that CTLA-4 negative signaling pathways maybe required for the induction of acquired tolerance. See p. 2148, 2nd column, Introduction.

Accordingly, in view of the combined teachings, it would have been obvious for the skilled artisan to modify the technique of producing antibodies in avian species, as taught by Ditullio, utilizing a construct encoding CTLA-4, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make such a modification, as the art recognizes the importance of suppressing CTLA-4 to generate acquired tolerance, for example.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-5, 7, 9-29, 62 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ditullio *et al.* (cited above) when taken with Mohammed *et al.* **This rejection is maintained for reasons of record, advanced in the prior Office action, mailed 11/16/05.**

Ditullio is described previously. Although Ditullio teach that the cell can be targeted *in vitro* or *in vivo*, they do not contemplate that the cell can produce an antibody outside of the context of producing a transgenic avian that produces the antibody. However, prior to the time the claimed invention was made, Mohammed teach expression of recombinant human antibodies in stably transfected DT40 cell lines. In particular, Mohammed teach that two types of vectors were developed, one with the heavy chain of the immunoglobulin which results in the expression of a murine anti-dansyl variable region joined to the appropriate human heavy chain constant region. The other vector encodes the light chain which results in the expression of a corresponding murine anti-dansyl variable region joined to a human kappa light chain constant region. [See pp. 116-117, bridging ¶]. Mohammed teach that these two vectors were co-transfected with each of the vectors into a chicken B lymphoblastoid cell line, DT40 [see p. 117, section 2.2.]. The transfected cells were maintained in culture media for two days, wherein surviving colonies were screened by ELISA to verify expression of the chimeric antibodies.

Accordingly, in view of the combined teachings, it would have been obvious for one of ordinary skill in the art, to use the cells and methods taught by Ditullio, and modify these methods to express a vector encoding an antibody by culturing a cell and isolating the antibodies from a cell, such as those contemplated by Ditullio, with a reasonable expectation of success. One of ordinary skill would have been sufficiently motivated to make such a modification, because cell lines expressing recombinant human antibodies could be used to inject into laying hens, in order to produce transgenic hens which express the antibody in their egg yolk. This expression would increase the yield of antibodies, and allow for simple purification of the protein. See also, Mohammed, Abstract.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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